the agent is internalized by the cells, wherein the cells are immune effector cells.

89. (Amended) The method of claim 57, wherein the chemokine receptor targeting agent is selected from the group consisting of IL-8, GCP-2, GRO-$\alpha$, GRO-$\beta$, GRP-$\gamma$, ENA-78, PBP, CTAP III, NAP-2, LAPF-4, MIG, PF4, IP-10, SDF-1$\alpha$, SDF-1$\beta$, SDF-2, MCP-1, MCP-2, MCP-3, MCP-4, MCP-5, MIP-1$\alpha$, MIP-1$\beta$, MIP-1$\gamma$, MIP-2, MIP-2$\alpha$, MIP-3$\alpha$, MIP-3$\beta$, MIP-4, MIP-5, MDC, HCC-1, LD78$\beta$, eotaxin-1, eotaxin-2, I-309, SCYA17, TARC, RANTES, DC-CK-1, lymphotactin, and fractalkine.

## REMARKS

A check for the requisite fee for a three month extension of time and additional claims accompanies this response. Any fees that may be due in connection with this paper or with this application may be charged to Deposit Account No. 50-1213. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 26-29, 31, 32, 34-37, 40, 42, 44-46, 48-54, 57 and 65-95 are pending in this application. Claim 38 is cancelled without prejudice or disclaimer. Claims 92-95, which find basis in the specification as originally filed, are added. Particular basis can be found, for example, at page 15, which recites that:

> Targeted immune effector cells include, but are not limited to, mononuclear phagocytes (MNPs), such as dendritic, microglial, monocyte and macrophage cells; leukocytes, such as basophils, neutrophils, and eosinophils; and lymphocytes, such as natural killer cells and T and B lymphocytes.

Claim 29 is amended to render it clear that the targeted chemokine receptor is on the immune effector cells. Claim 35 is amended to provide proper antecedent basis for claim 36, and claim 89 is amended to depend from a pending claim. Therefore no new matter is added.

Marked-up amended claims pursuant to 37 C.F.R. §1.121 are attached hereto.

Also ~~pr~~ovided is a an unexecuted DECLARATION of Dr. McDonald, which provides an analysis of disclosure and teachings of the cited reference. The executed DECLARATION will be provided upon receipt. The DECLARATION, while not necessary for such analysis, provides a cogent discussion of the disclosure and teachings of Roby *et al.* and discusses supporting references to aid in a proper interpretation of the cited reference. Also attached are references that support arguments set forth below and in the DECLARATION.

**THE REJECTION OF CLAIMS 26-29, 31, 32, 34-38, 40, 42, 44-46, 48-54, 57 and 65-91 UNDER 35 U.S.C. §112, FIRST PARAGRAPH**

Claims 26-29, 31, 32, 34-38, 40, 42, 44-46, 48-54, 57 and 65-91 are rejected under 35 U.S.C. 112, first paragraph, because:

> the specification, while enabling for a method of producing cytotoxicity by contacting cells with a chemokine-toxin conjugate in vitro, allegedly does not reasonably provide enablement for a method of treating a pathological condition by administering a chemokine-toxin conjugate *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In the current Office Action, the Examiner states that the Declaration filed in response to the previous Office Action is not persuasive to demonstrate enablement "since enablement must be demonstrated in the specification as originally filed." It is respectfully submitted that this is incorrect. The specification must teach one of skill in the art to make and use that which is claimed, which the instant specification does. The DECLARATION does not teach how to make and use what is claimed, but was provided to demonstrate that the conjugates function as claimed in light of the apparent doubt thereof expressed by the Examiner. There is no requirement for an application to address future rejections nor to provide *in vivo* data (see the PTO Guidelines and cases cited therein). The specification as filed teaches how to make and how to use conjugates in methods as claimed without undue experimentation.

The Office Action further alleges that the application does not enable one of skill in the art to treat all pathological conditions by treating the underlying pathology and undue experimentation would be required to practice the claimed subject matter. As discussed previously and demonstrated in the DECLARATIONs of record, the instant methods are based upon treatment of a common underlying pathology that is shared by a variety of disorders. All methods target immune effector cells involved in the pathologies. The DECLARATIONs of record as well as the specification as filed demonstrate that immune effector cells are targeted. The specification teaches how to select particular chemokine targeting agents and provides pages of and pages of exemplification. The claims are not directed to treating all pathologies, but to modulating the activity of immune effector cells, which are involved in a variety of pathological conditions. The methods are directed to targeting immune cells and to thereby treat the inflammatory pathology. The specification establishes and those of skill in the art know that a variety of different disorders share this common underlying pathology. Recitation of a particular disease goes to selection of the subjects to be treated.

Accordingly, this rejection is respectfully traversed. It is noted, that the standard for enablement does not require *in vivo* data but requires that the specification teach one of skill in the art to make and use the subject matter as claimed. In this instance, the specification does teach how to select chemokine targeting agents, how to prepare the conjugates and how to administer them. As discussed in previous responses the specification teaches one of skill in the how to select targeting agents for particular diseases and at particular stages thereof.

Furthermore, the Declarations of record demonstrate that the conjugates have activity *in vivo* and *in vitro*. There is no requirement that there must be working examples in an application; a specification is presumed enabled. Furthermore, the specification and Declarations of record demonstrate that the

conjugates are targeted to immune effector cells, particularly activated leukocytes and that the diseases intended for treatment share the same underlying pathology. The comments of the Examiner are discussed in turn below.

**RELEVANT LAW**

To satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be met by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of § 112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." *In re Marzocchi et al.*, 469 USPQ 367 (CCPA 1971)(emphasis added).

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." *In re Grimme, Keil and Schmitz*, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. *Smith v. Snow*, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

Thus, there is no requirement for disclosure of every species within a genus. Applicant is entitled to claims are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

**PTO GUIDELINES**

The standard for determining whether the specification meets the enablement requirement is whether it enables any person skilled in the art to make and use the claimed subject matter without **undue** experimentation. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1999) (emphasis added). In determining whether any experimentation is "undue," the above-noted factors are to be considered.

As instructed in the published PTO guidelines, it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The analysis must consider all the evidence related to each of the factors, and any conclusion of non-enablement must be based on the evidence as a whole. *Id.* 8 USPQ2d at 1404 & 1407.

The starting point in an evaluation of whether the enablement requirement is satisfied is an analysis of each claim to determine its scope. As set forth in the guidelines, all questions of enablement are evaluated against **the claimed subject matter**. The focus of the inquiry is whether everything within the scope of the claim is enabled. With respect scope of enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *In re Moore,* 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). Once the scope of the claims is addressed, a determination must be made as to whether one skilled in the art is enabled to make and use the entire scope of the claimed subject matter without undue experimentation.

**Analysis**

As discussed in detail, previously and herein, the level of skill and knowledge of those who practice in this art, the guidance in the specification, the fact that the claims parallel the disclosures, and the nature of the experimentation, which is routine, as well as the evidence and information in the and the DECLARATIONs of record in the application, lead to the conclusion that it would not require undue experimentation to practice the claimed methods.

**The rejected claims**

All claimed methods employ conjugates that contain a chemokine receptor targeting agent to target an agent to immune cells that express chemokine receptors. The methods are methods of treatment by inhibiting proliferation, activation or migration of immune cells.

To focus of the remarks herein, subject matter of the claims, particularly the independent claims is summarized:

Claim 29 is directed to a method for treating pathological conditions by treating the underlying pathology associated with inflammatory responses and secondary tissue damage associated with activation, proliferation and migration

of immune effector cells by inhibiting activation, proliferation or migration of immune effector cells, by:

> administering a conjugate to an animal whereby activation, proliferation, migration of the immune effector cells is inhibited.

The conjugate contains:

> a targeted agent or a portion thereof and a chemokine receptor targeting agent or a portion thereof sufficient to bind to the chemokine receptor on immune effector cells and facilitate internalization of the conjugate,
>
> where:
>
> the chemokine receptor targeting agent is a chemokine, an antibody that specifically binds to a chemokine receptor or a fragment of the chemokine or antibody
>
> the chemokine, antibody or fragment thereof binds to the receptor and internalizes the targeted agent in a cell
>
> the targeted agent or portion thereof, when internalized in a cell, alters metabolism or gene expression in the cell, regulates or alters protein synthesis in the cell, inhibits proliferation of the cell or kills the cell
>
> the conjugate binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor.

Claim 35 is directed to methods of targeted delivery an agent into cells that express chemokine receptors by:

> associating the agent with a chemokine receptor targeting agent, whereby:
>
> the *chemokine receptor targeting agent binds to a chemokine receptor* expressed on the cells; and
>
> the agent is internalized by the cells. The cells are immune effector cells.

Claim 40 is directed to a method for treating secondary tissue damage and associated disease states by:

> administering to a subject in need thereof an effective amount of a therapeutic agent that inhibits the proliferation, migration or physiological activity of secondary tissue damage-promoting inflammatory cells, wherein the therapeutic agent is a conjugate that comprises a chemokine receptor targeting agent and a targeted agent or portion thereof selected so that conjugate binds to a chemokine receptor and internalizes the targeted agent, which inhibits the proliferation, migration or physiological activity of the secondary tissue damage-promoting cells.

Claim 72 is directed to methods of inhibiting proliferation, migration or activation of immune cells by:

> contacting immune cells with a conjugate that comprises a targeted agent or a portion thereof and a chemokine receptor targeting agent whereby activation, proliferation, migration of the immune cells is inhibited, wherein:
>
> the targeted agent or portion thereof is a toxin;
>
> the chemokine receptor targeting agent is a chemokine or a fragment of thereof that binds to a chemokine receptor and internalizes the targeted agent; and
>
> *the conjugate binds to a chemokine receptor* resulting in internalization of the targeted agent in cells bearing the receptor.

Claim 86 is directed to methods for treatment of inflammatory disorders:

> A method of treating a disease or disorder associated with an inflammatory response by:
>
> *identifying immune cells that are activated in the disease or disorder;*
>
> identifying chemokine receptors expressed on the cells;
>
> preparing a conjugate or plurality thereof containing toxin linked to a chemokine or a plurality of chemokines that specifically bind to the identified chemokine receptors and effect or facilitate internalization of the toxin into the cells; and
>
> *contacting the immune cells with the conjugate or plurality thereof.*

As discussed in the previous DECLARATION of record, chemokine receptors are expressed on a particular defined subset of cells, whose role in inflammatory responses and secondary tissue damage are known. The specification describes how to select chemokines for a particular immune cell type.

**1. A Generic treatment modality is provided by the instant application**

The instant application provides a generic method for treating an underlying pathology common to a variety of disorders and thereby provides a way to treat or prevent such disorders. The specification describes in great detail the chemokine system and teaches how to exploit it for treatment or prevention of inflammatory responses common to a variety of disorders. As described in the application and DECLARATIONs of record, the chemokine system provides a finely-tuned system that can be exploited for such methods.

As described in the DECLARATIONs of record and the application, the chemokine system is ideal for exploitation in this manner. There are a variety of different chemokine receptors and chemokine receptor targeting agents. Chemokine receptors are elevated in a variety of pathologies and are elevated in patterns characteristic of a particular disease and in a temporal manner in a disease. As a result, chemokine receptor targeting agents conjugates can be prepared as taught in the application by selecting a targeting agent that targets receptors on cells that are activated, migrate or proliferate in a particular disease. The application details how such selection is to be made. The data in the application and DECLARATIONs of record show that the conjugates target the selected receptors and are cytotoxic to the targeted cells in recognized *in vitro* and *in vivo* models.

This concept and claimed methods are generically described and claimed. As noted above, "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." *In re Grimme, Keil and Schmitz*, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. *Smith v. Snow*, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

There is no requirement for disclosure of every species within a genus. Applicant is entitled to claims are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

In this instance, **the application discloses and claims a generic treatment modality; the applicant has disclosed as "a generic invention" and has provided persuasive evidence that it functions as claimed.** Therefore, applicant has fulfilled the requirements of § 112, first paragraph "by broad terminology." *In re Marzocchi et al.*, 469 USPQ 367 (CCPA 1971)(emphasis added), and as discussed below, numerous detailed examples.

**2.** The Examiner states:

> Applicants provide a Declaration and argue that this information provides a nexus between in vitro and in vivo data. Applicants also provide numerous references showing that a mouse xenograft model is a recognized model that is used to assess the in vivo efficacy of antitumor agents and that immunotoxins and cytotoxic conjugates have been widely shown to possess pharmacological activity. Applicants also argue on page 25 of the response that chemokine receptors are elevated in a variety of pathologies and are elevated in patterns characteristic of a particular disease and in a temporal manner in a disease and that the instant application provides sufficient evidence that chemokine-receptor targeting conjugates possess specificity for, and activity against, target chemokine-receptor-hearing cells.
>
> The Examiner urges that the data disclosed in this Declaration are not persuasive to demonstrate enablement "since enablement must be demonstrated in the specification as originally filed. There is no data in the original specification showing that any of the chemokine-toxin conjugates have any affect on activated immune effector cells in vivo." Applicants have only shown that some of these conjugates are active in an RIP assay (Example 2). Although there is discussion of a mouse xenograft model, there is no experimental data provided. The Examiner erroneously concludes that the Declaration after the fact cannot be used to establish enablement at the time of filing.

The specification teaches how to practice the methods as claimed; the provision of data was for demonstrating that the conjugates function as claimed in light of the doubt expressed by the Office The DECLARATIONs do not provide enablement, but demonstrate operability, which can be established with data obtained at any time. The standard of enablement is whether the specification at the time of filing teaches one of skill in the art to practice what is claimed. The DECLARATIONs employed the methods and conjugates provided in the

application and demonstrated that **AS TAUGHT** in the application, the conjugates specifically target immune effector cells *in vitro* and *in vivo* as **taught** in the application. There is nothing in the DECLARATIONs that is not provided in the application as filed.

As discussed in the previous responses and DECLARATIONs of record and as shown in the application, chemokine receptors are expressed on a particular defined subset of cells, whose role in inflammatory responses and secondary tissue damage are known. The specification describes how to select chemokines for a particular immune cell type.

The DECLARATIONs and application demonstrate that exemplary conjugates are targeted as described and claimed in this application and are cytotoxic to the targeted cells **as described in the specification**. There is no basis upon which to conclude that any other conjugates prepared as described in the application would fail to exhibit the targeting and cytotoxicity.

As discussed in the previous response which cited numerous publications by those of skill in this art, the *in vitro* tests and *in vivo* described in the instant application and DECLARATIONs of record have been recognized to establish that immunotoxins and cytotoxic conjugates possess pharmacological activity that supports a finding of practical utility. In *In re Hartop*, 311 F.2d 249, 135 USPQ 419, 426-7 (CCPA 1962), the Court held that, when one skilled in the art would accept a particular test or experiment as being reasonably predictable that a tested invention would operate as alleged or have the therapeutic effect as alleged, the burden on behalf of an applicant had been satisfied. The Court went on to note that Congress has assigned the task of protecting the public from the advertising, use and sale of harmful drugs to the Food and Drug Administration (FDA), and the Federal Trade Commission, not the U.S. Patent and Trademark Office.

The instant specification and DECLARATIONs of record demonstrate using *in vitro* and *in vivo* models that the chemokine receptor targeting

conjugates are toxic to cells that express receptors targeted by the selected chemokine receptor targeting. In addition, the specification and DECLARATIONs show that the conjugates are not toxic to cells that do not exhibit an upregulation of such receptors or that do not express such receptors.

As shown in the specification, and in the DECLARATIONs, three exemplary and different conjugates OPL98110 (an MCP-1-Shiga toxin conjugate), OPL98111 (an SDF-1$\beta$-shiga toxin conjugate), and OPL98112 (an eotaxin-shiga toxin conjugate) specifically target and are cytotoxic to cells that are known to bear chemokine receptors specifically recognized by the targeting agent in each conjugate. This cytotoxicity and specificity is demonstrated in recognized *in vitro* assays and also in two instances in mouse xenograft models.

As taught in the specification MCP-1 specifically binds to CCR2 receptors, which are present in the activated microglial cells in the CNS. Given its profile of cell and receptor selectivity OPL98110 (MCP-1, CCR2) is an appropriate chemokine-toxin conjugate for use in the nervous system. The result in the DECLARATION demonstrate that it targets cells of monocytic lineage including THP-1 leukemia cells, primary human peripheral blood mononuclear cells (PBMCs) and T-cells. Other experiments, as described in the DECLARATION, demonstrated that this conjugate targets cells of monocytic lineage (i.e. THP-1 cells which are microglia and MNP-like) as well as human peripheral blood monocytes and T-cells, but not primary human neurons or U251 cells (a glioma of astrocytic lineage). OPL98110 was shown to bind to only to activated proliferating monocytes.

The over-expression of MCP-1 and target receptors have been observed in a wide range of cancers. For, example MCP-1 is responsible for the large leukocyte infiltrates seen in breast, lung and ovarian cancers. MCP-1 has been shown to play a direct role in tumor associated angiogenesis (a first for an $\alpha$-chemokine family member) and tumor progression. Consistent with this

OPL98110 was found to be highly toxic to MCF-7 breast carcinoma cells in culture.

OPL98111 is conjugate that contains $\alpha$-chemokine SDF-1$\beta$, which only binds to CXCR4 receptors. As described in the DECLARATION, the chemokine-toxin OPL-98111 (SDF-1$\beta$) targets U251 (astrocytoma), HT-29 (human colon carcinoma), and THP-1 (monocytoid leukemia) cells in culture (Figure 1, attached hereto), as well as primary human monocytes, T-cells, and primary human neurons, which all are known to express the targeted receptor. Figure 1 in the DECLARATION shows the cytotoxic activity of OPL-98111 on target cancer cells in culture. The data show that only the activated population of isolated monocytes (*i.e*, those with upregulated CXCR4 expression) are targeted.

The activity of OPL98112 was also demonstrated in a mouse xenograft model of human colon carcinoma cells, which are known to express the targeted receptor. OPL-98111 retarded tumor growth relative to control animals. Figure 2 attached to the DECLARATION shows the effects of the conjugate on the tumors in the animals. The Figure shows that tumors from treated animals exhibited far less live tumor mass than untreated animals. In addition, the tumors in the untreated animals showed greater vascularization. Also, in the treated animals, the tumors contained abundant monocytic cells, which clear cellular debris.

OPL98112, a fusion of eoxtaxin and shiga toxin, was also tested in a mouse xenograft model and shown to be non-toxic. Activity to the targeted receptors was demonstrated in *in vitro* cytotoxicity assays, showing a dose response in proliferating monocytes.

Thus, there is data of record that shows that these conjugates **function as described in the application**. The DECLARATIONs of record do not provide the enablement, but demonstrate operability and meet the standards for such

demonstration set by the courts and accepted by the Patent Office. The DECLARATIONs show that **as taught and described in the applications** conjugates **provided in the application** specifically target activated cells of the immune system and other cells that are known to express the targeted receptors. They are well-tolerated in animal models and shown to have *in vivo* activity.

Other toxin conjugates and immunotoxins that exhibit similar (or less) potency and specificity are recognized by those of skill in this art to be useful in methods of treatment. These conjugates manifest *in vitro* activity comparable to or less than the instantly claimed . A lengthy list and description of such references and the conjugates described therein was included in the previous response. In addition, the previous response demonstrate that the mouse xenograft model is an accepted model to demonstrate effectiveness of conjugates. Such model was not provided in the DECLARATIONs to "enable" the claimed methods, but to demonstrate that the conjugates function as described in the application, which teaches how to make and use the conjugates and practice the claimed methods. As stated in *Nelson v. Bowley*, the Court of Customs and Patent Appeals held that tests establishing pharmacological activity, such as the stimulation of smooth muscle tissue from gerbil colons and the modulation of the blood pressure in rats, manifest a practical utility. 206 USPQ 881 (CCPA 1980); *In re Bundy* 209 USPQ 48 (CCPA 1981). Therefore, the results set forth in the DECLARATIONs of record clearly establish a pharmacological effectiveness sufficient to meet the requisites of 35 U.S.C. §112, first paragraph.

Furthermore, having shown targeting of the conjugates there is no reason to doubt the efficacy of the conjugates eliminating targeted cells. As discussed in previous responses, there are conjugates that have demonstrated efficacy that target immune cells. The are numerous examples that demonstrate that elimination of immune cells in various diseases is a valid approach to therapy.

Elimination in such methods is effected by different means and, thus, do not teach the eradication of such cells by using agents that exploit chemokine receptors or their ligands as claimed in this application.

As stated in the previous responses, the beauty of the chemokine system that the instant application and instantly claimed methods exploit, is that there is a greater deal of targeting specificity and versatility than in prior art methods. For example, as taught in the application, CCR3 expressing TH2 cells and eosinophils are implicated in the pathology of allergic asthma. As described in the application, a conjugate of a toxin with the eotaxin ligand (OPL98112) can be sued to eliminate both types of pathological cells; whereas an antibody can only eliminate on type or the other. OPL98112 exhibits no gross toxicity *in vivo* using normal animals (mentioned above).

Since the instantly claimed conjugates process activity in similar *in vitro* and *in vivo* assays, those of skill in the art would, in light of the above patents and publications and numerous others, recognize that the *in vitro* data provided in this application provides sufficient evidence to support a conclusion that the conjugates are useful in methods of treatment as claimed. Those of skill in this art certainly would recognize that the instant application provides sufficient evidence to conclude that chemokine-receptor targeting conjugates possess specificity for and activity against target chemokine-receptor bearing cells and that these conjugates will function *in vivo* as claimed and as described in the instant application.

**3. The Examiner continues:**

Furthermore, even if this Declaration was persuasive, Applicants would still not be enabled for treating all pathological conditions by treating the underlying pathology. Beginning on page 26 of the response filed 10/15/02, Applicant argues that a considerable amount of experimentation is permissible particularly if it is routine. Applicants argue that the breadth is not excessive, that the skill in the art is high, that the specification discusses in great detail that the activation, migration and proliferation of leukocytes are the hallmark of a vast number of immunomodulatory diseases and that the specification provides sufficient

> guidance and working examples of receptors and agents involved with treatment of numerous diseases. Diseases that Applicants claim are treatable with their claimed methods can be seen in claims 31 and 32. This list, respectfully, is a comprehensive laundry list of immune diseases and there is no guidance in the specification as to how one would go about treating each of these diseases.
>
> Though these diseases may all involve leukocytes, the pathologies are not identical, since they are all different diseases and would require different modes of intervention.

It is respectfully submitted that the Examiner's statements are without merit. The instantly claimed methods treat all of the pathologies by employing the same generic mode of intervention, targeting of immune cells. As discussed in detail previously, the specification outlines how one identifies the particular conjugate to use and provides numerous examples (see *e.g.*, the Tables in the specification describing which type of immune cell is elevated in what disorders and which chemokines target such cells).

Furthermore, the claims are not directed to treating particular pathologies. The claims recite, for example, :

> The method of claims 29, wherein the treated pathology underlies a disorder or disease state that is selected from the group consisting of CNS injury, CNS inflammatory diseases, neurodegenerative disorders, heart disease, inflammatory eye diseases, inflammatory bowel diseases, inflammatory joint diseases, inflammatory kidney or renal diseases, inflammatory lung diseases, inflammatory nasal diseases, inflammatory thyroid diseases, inflammatory responses associated with bacterial or viral infections and cytokine-regulated cancers.

Hence, the treated pathology is the same. The disorder identifies subjects who are candidates for treatment.

**4. The Examiner states:**

> Applicants provide a long list of toxins in the specification (Table 4 and pages 8 1-82) are claiming the use of a large list of chemokines (claim 68) and chemokine receptors (claims 70 and 71), but there is no guidance of which combinations of the toxins and conjugates to use for which disease.

> The number of possible combinations of chemokines and toxins is immense. Applicants argue that selection of this chemokine pathway is not new and that the specification details a variety of diseases and identifies the appropriate receptors to target. Applicants argue that this information, coupled with the exemplification of a dozen different conjugates in the specification, provides more than adequate guidance to practice the claimed invention. These arguments have also been considered, but are not deemed persuasive.

It is respectfully submitted that this is not correct. The specification exemplifies synthesis of about a dozen conjugates, but provides detailed guidance of selection of which chemokine targeting agents to use to target a particular immune cells (see, Tables 1-6 and the detailed description). In addition, the specification demonstrates that the pathological immune cells for a variety of disorders are known. The specification teaches cells are targeted by a particular chemokine and demonstrates that such knowledge is known by those of skill in the art. The specification teaches cells that express receptors for particular chemokines and demonstrates that such knowledge is known by those of skill in the art, and teaches the immune cells involved in a particular pathology and demonstrates that such knowledge is known by those of skill in the art. These details constitute the bulk of the specification, which is close to 200 pages long. The combination of this information provides those of skill in the art the ability to practice the methods as claimed. The specification by specifically listing chemokines, their receptors and cells that express such receptors and diseases in which such cells are involved does not merely exemplify twelve conjugate, but hundreds of conjugates and the use thereof to treat or prevent the underlying inflammatory pathology of many diseases and disorders.

**5. The Examiner continues:**

> Applicants may have disclosed numerous conjugates in the specification, but they nave not shown that these conjugates are effective in vivo to treat the underlying pathology of any disease. The fact that conjugates and the mouse xenograft model were known at the time of the present invention does not enable the

> present invention. Applicants have only shown in the Declaration that two compounds are effective in a mouse xenograft model. Applicants, respectfully, are claiming a magic bullet to treat all diseases with an underlying pathology. However, according to a paper cited by the Applicants (Idrugs 4(4):427-442, 2001), in which the present inventor is an author, it is stated that a few generalizations about chemokines prove to be entirely valid (i.e. it is unpredictable; page 431, right column, last paragraph).They also state that it is important to establish the biological and clinical profile of a given chemokine on a case-by-case basis. This is especially true if the ratio, absolute number, and activation status of the chemokines target cells change during the course of the injury or disease. Therefore, not only have Applicants not enabled the treatment (e.g. which conjugates to use) for the expansive number of diseases,but they have also not taught (only speculated) how to alter this treatment regimen, or when and which conjugates to use throughout the treatment period, given that the treatment (i.e. types of conjugates)would likely need to change.

It is respectfully submitted that this is an improper characterization of the application and Dr. McDonald's publication. The application and claims are not directed to a "magic bullet" but describe a way of harnessing and exploiting a system of immune regulation (the chemokines) and to thereby intervene in the inflammatory process by targeting immune cells that express receptors. This is a generic concept that is clearly disclosed in the application, which teaches how to exploit the chemokine system for treating inflammatory processes that underlie particular disorders. The DECLARATIONs of record demonstrate that as described in the application, targeting chemokine receptors provides a means to specifically target cells that express such receptors. There is no requirement nor any need to demonstrate this over and over again.

In the IDrugs paper, Dr. McDonald states, for example, page 435, cols. 1-2) that chemokine-toxin fusion proteins target cells with specificity and that these agents distinguish between activated and quiescent cells, and states that given the knowledge of the:

> temporal and spatial participation of chemokines, chemokine receptors and leukocyte subtypes in disease and trauma, we suggest that specific

> chemokine-toxins would be effective in treating a wide array of conditions as illustrated in Table 5.

The paragraph on page 431 of the paragraph, cited by the Examiner, does not state that the instantly claimed methods do not work or that they are unpredictable, but merely states that chemokines as a class have a variety of activities and that their levels and target cells are not constant throughout the course of a disease. One of the points of the paper and the application (and also discussed in the DECLARATIONs of record) is that this variation in chemokine level and target cell level can be exploited in the claimed methods to finely tune treatment for a particular disease. As stated, it is possible by virtue of the methods and conjugates provided in the application to select a conjugate based upon the progression of a particular disease. The cited paragraph states that for a particular chemokine, its profile and expression should be determined empirically if one is to best exploit the technology.

The same page of the article states that Osprey (the assignee of the instant application) has designed chemokine-toxins that avoid problems of the first-generation ligand toxins. The approach (that described and claimed in the instant application) is to (page 431, col 1):

> utilize the large number of chemokine ligands and the elevation of specific chemokine receptors to design therapeutic agents that selectively target discrete populations of diseased cells. Disease-selective upregulation of specific chemokine receptors increases the likelihood of targeting specific cell populations in a chemokine-specific manner and a relatively low drug concentrations. Furthermore, the exact chemokine-toxin can be changed to suit the stage and severity of the disease . . ..

Hence the cited paragraph, taken out of context, is merely a cautionary note for designing conjugates according to the methods of the application (that are reported in the IDrugs publication).

**6. The Examiner continues:**

> Furthermore, there is a lack of guidance and working examples in the specification as originally filed with regards to the use of these conjugates in treating any disease in vivo. These, along with the lack of predictability to the artisan which conjugates to use for what diseases and at what

point in the treatment, leads the Examiner to maintain that undue experimentation would be necessary to practice the invention as claimed.

As noted, the application provides pages and pages of details teaching how to make and use the conjugates. For example, the Examiner's attention is directed to pages 98-118, which detail how to make the conjugates and pages 142-151, which detail formulation and administration of compositions containing the conjugates.

As discussed and demonstrated in the previous responses, the level of skill and knowledge of those who practice in this art, the guidance in the specification, the fact that the claims parallel the disclosures, and the nature of the experimentation, which is routine, as well as the evidence and information in the DECLARATIONs of record in the application, lead to the conclusion that it would not require undue experimentation to practice the claimed methods.

As noted previously, the inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

**(A) The breadth of the claims**

As discussed above, all of the rejected claims are directed to methods in which conjugates that contain a chemokine receptor targeting agent bind to chemokine receptors on targeted cells to internalize a linked agent, such as a cytotoxin.

As discussed below and above, the application broadly and in great detail describes how to select chemokine receptor targeting agents and how to prepare targeting agent conjugates and how to use them therapeutically. Thus, the claims are of the same scope as the disclosure.

**(B) The relative skill of those in the art**

The level of this of those in this art is recognized to be high (see, , *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986). Also, the prior patents and publications in this art (see, *e.g.*, those listed above, and those of record in this application), which are directed to those of skill in this art, are authored by those with advanced degrees and require a high level of skill and education to comprehend. Such publications, thus, evidence the high level of skill of those who work in this art.

**(C) Teachings in the specification**

As described in the application in great detail and summarized in the previous responses and discussed in the DECLARATIONs, the activation, migration and proliferation of leukocytes are the hallmark of a vast number of immunomodulatory diseases. These cells are responsible for the production of inflammatory mediators and toxic molecules (such as cytokines, reactive oxygen species, metalloproteinases and cytotoxins) that are essential for the host immune defense against invading pathogens, such as bacteria and viruses. Inappropriate triggering, disregulation or over-activation of the immune response is responsible for the damage to normal host tissue witnessed in leukocyte-mediated diseases such as arthritis, multiple sclerosis, and pulmonary diseases. Leukocyte-mediated diseases also include trauma (e.g. spinal cord injury) and cancers and others. In the latter, leukocytes exert tumorigenic effects by nourishing the cancer directly or indirectly (by directing angiogenesis), by supplying chemokines and growth factors, and aiding metastasis by supplying various extracellular proteases.

Thus leukocytes are the mediators of diseases that can have combinations of allergic, autoimmune, angiogenic, inflammatory, and tumorigenic components. It must be noted that leukocytes are not necessarily the trigger of disease (which may be viral , bacterial, allergen, aberrant gene expression, trauma etc – initiated) but the excess immune (leukocyte) response is responsible for disease manifestation and progression.

This application provides an avenue of the therapeutic intervention that exploits this common underlying response (termed an underlying pathological response in the claims). Selection of this pathway for therapeutic intervention is not new (see discussion below); what is new in this application is the mode of intervention. The instant application provides conjugates that are targeted to specific chemokine receptors. (see, *e.g.*, Arimilli *et al.* (2000) *Immunological Rev. 177*:43-51).

The instant inventors recognized that chemokines play an intimate role in these varied diseases, and, as described in the application, provide a large repertoire of molecules that interact with an array of receptors. It is the instant inventors who have identified chemokine receptors as ideal targets for delivery of therapeutics, such as toxins.

Having provided the mode of intervention, the use of chemokines as targeting agents as described herein, one of skill in the art will recognize by virtue of knowledge in the art and the disclosure in the application, that the method provides a means for treatment of any disease in which in inappropriate triggering, disregulation or over-activation of the immune response is involved.

**(D) The amount of direction or guidance presented, the presence of working examples, the nature of the invention, and predictability**

The instant specification exemplifies and provides detailed instructions regarding how to make and use chemokine receptor targeting agent conjugates. The specification details a variety of diseases and identifies the receptors to target in each disease and also identifies agents that target the receptors.

The application exemplifies and details construction of 12 conjugates (see, *e.g.*, Table 6 and accompanying text and Examples). The specification teaches (and the DECLARATIONs also describe) how to make the conjugates, and, as how to select chemokine receptor targeting agents and details the specificity of a dozen or more exemplary conjugates. The specification also provides details of *in vitro* and *in vivo* models to test conjugates (see, page 110 *et seq.*, which provides details of models for a variety of diseases) and teaches how to formulate the conjugates for administration (page 132 *et seq.*).

The DECLARATIONs demonstrate that exemplary conjugates possess specificity and cytoxicity for targeted cells *in vitro* and *in vivo*, and do not exhibit toxicity *in vivo*. The previous DECLARATIONs and the application establish that the diseases are associated with activation, proliferation and migration of immune effector cells, including secondary tissue damage-promoting cells, and, thus, share a common underlying pathology. This coupled with the data in the DECLARATIONs, the detailed description in the application regarding specificity of a large number of chemokine targeting agents and exemplification of a dozen different conjugates with a description of each conjugate's specificity, provides more than adequate guidance to practice the claimed methods.

It would only require routine experimentation to prepare conjugates as described in the application and use them in the claimed methods. The data provided and description demonstrate the each conjugates targets the intended cells and is cytotoxic. Hence there is no issue of unpredictability.

**(E) The state of the prior art**

Also, as evidenced and discussed above, although the instant inventors are the first to exploit the chemokine system in this manner, the art is replete with examples of successful uses of cytotoxic conjugates and immunotoxins. The instantly claimed conjugates exhibit cytotoxicity and targeting specificity

comparable to or greater than other cytotoxic conjugates and immunotoxins, and, thus there is no reason to doubt that they will possess *in vivo* activity.

**Conclusion**

Therefore, in light of the fact that the claims are tailored to the scope of the disclosure, the high level of skill in the art, the knowledge and extent of the prior art, the instant disclosure, which provides detailed guidance for selecting chemokine receptor targeting agents and numerous examples of conjugates, it would not require undue experimentation to practice the claimed methods.

**THE REJECTION OF CLAIMS 26-29, 34-38, 40, 44-46, 48-54, 57, 65-91 UNDER 35 U.S.C. §102(b) or 103(a)**

Claims 26-29, 34-38, 40, 44-46, 48-54, 57, 65-91 are rejected under 35 U.S.C. § 102(b) as being anticipated by Roby *et al.* or under 35 U.S.C. § 103(a) as being obvious over Roby *et al.* Roby *et al.* describes conjugates that contain a C-terminal portion of MGSA/GRO$\alpha$ linked to daunorubicin for treating melanoma. The Examiner states that the burden is on the applicant to demonstrate that the conjugate of Roby *et al.* does not bind to receptors on activated leukocytes and/or that it is not internalized.

This rejection is respectfully traversed insofar as it applies to the rejected claims and to new claims 92-94. The attached DECLARATION of Dr. McDonald and the arguments below and the attached references demonstrate that the conjugates of Roby *et al.* cannot and do not bind to chemokine receptors, including chemokine receptors present on activated leukocytes, and are not internalized upon interaction with the melanoma cells targeted by Roby *et al.*

Furthermore, the claims in this application are directed to methods for inhibiting activation, migration and proliferation of immune effector cells and/or for targeting agents to immune cells that express chemokine receptors. Even if the conjugates of Roby *et al.* bound to chemokine receptors on melanoma cells and were internalized, Roby *et al.* does not disclose, teach or suggest methods for or methods involving inhibiting activation, migration and proliferation of immune effector cells or targeting of such cells. Melanoma cells are not immune

cells. Thus, the disclosure and/or teachings of Roby *et al.* is virtually irrelevant to the instant claims.

**The claims**

To focus of the remarks herein, subject matter of the claims, particularly the independent claims is summarized:

Claim 29 is directed to a method for treating pathological conditions by treating the underlying pathology associated with inflammatory responses and secondary tissue damage associated with activation, proliferation and migration of immune effector cells by inhibiting activation, proliferation or migration of immune effector cells, by:

> administering a conjugate to an animal whereby activation, proliferation, migration of the immune effector cells is inhibited.

The conjugate contains:

> a targeted agent or a portion thereof and a chemokine receptor targeting agent or a portion thereof sufficient to bind to the chemokine receptor on immune effector cells and facilitate internalization of the conjugate,
>
> where:
>
> the chemokine receptor targeting agent is a chemokine, an antibody that specifically binds to a chemokine receptor or a fragment of the chemokine or antibody
>
> the chemokine, antibody or fragment thereof binds to the receptor and internalizes the targeted agent in a cell
>
> the targeted agent or portion thereof, when internalized in a cell, alters metabolism or gene expression in the cell, regulates or alters protein synthesis in the cell, inhibits proliferation of the cell or kills the cell
>
> the conjugate binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor.

Claim 35 is directed to methods of targeted delivery an agent into cells that express chemokine receptors by:

> associating the agent with a chemokine receptor targeting agent, whereby:
>
> the *chemokine receptor targeting agent binds to a chemokine receptor* expressed on the cells; and
>
> the agent is internalized by the cells. The cells are immune effector cells.

Claim 40 is directed to a method for treating secondary tissue damage and associated disease states by:

> administering to a subject in need thereof an effective amount of a therapeutic agent that inhibits the proliferation, migration or physiological activity of secondary tissue damage-promoting inflammatory cells, wherein the therapeutic agent is a conjugate that comprises a chemokine receptor targeting agent and a targeted agent or portion thereof selected so that conjugate binds to a chemokine receptor and internalizes the targeted agent, which inhibits the proliferation, migration or physiological activity of the secondary tissue damage-promoting cells.

Claim 72 is directed to methods of inhibiting proliferation, migration or activation of immune cells by:

> contacting immune cells with a conjugate that comprises a targeted agent or a portion thereof and a chemokine receptor targeting agent whereby activation, proliferation, migration of the immune cells is inhibited, wherein:
>
> the targeted agent or portion thereof is a toxin;
>
> the chemokine receptor targeting agent is a chemokine or a fragment of thereof that binds to a chemokine receptor and internalizes the targeted agent; and
>
> *the conjugate binds to a chemokine receptor* resulting in internalization of the targeted agent in cells bearing the receptor.

Claim 86 is directed to methods for treatment of inflammatory disorders:

> A method of treating a disease or disorder associated with an inflammatory response by:
>
> *identifying immune cells that are activated in the disease or disorder*;
>
> identifying chemokine receptors expressed on the cells;
>
> preparing a conjugate or plurality thereof containing toxin linked to a chemokine or a plurality of chemokines that specifically bind to the identified chemokine receptors and effect or facilitate internalization of the toxin into the cells; and
>
> *contacting the immune cells with the conjugate or plurality thereof*.

All claimed methods employ conjugates that contain a chemokine receptor targeting agent to target an agent to immune cells that express chemokine receptors. The methods are methods of treatment by inhibiting proliferation, activation or migration of immune cells.

**1. Anticipation**

**Relevant law**

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), *cert. denied*, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

**Differences between the disclosure/teachings of the cited reference and claimed subject matter**

Roby *et al.* describes preparation of a conjugate that contains a C-terminal portion of MGSA/GRO*α* peptide conjugated to daunorubicin. Roby *et al.* shows that the conjugates have "activity" on melanoma cells. Roby *et al.* states that it is known that the N-terminal portion of the polypeptide is necessary for binding to neutrophils (immune cells) and states (see, Roby *et al.* (1995) *Biochem. Biophys. Res. Commun. 206*:792-798, cited in Roby *et al.* and provided with this response and of record in the application), that the C-terminal portion of MGSA/GRO*α* peptide appears to bind to a receptor on melanoma cells that is different from the receptor to which it (and its analog IL-8) binds on neutrophils.

As described in Roby *et al.* and also as discussed in the attached DECLARATION and articles cited therein, the C-terminal peptide of MGSA/GRO*α* does not bind to chemokine receptors. Furthermore, this is evidenced in Roby

*et al.*, since the conjugate does not bind to SKOV-3 cells. As described in the DECLARATION and as evidenced in the attached papers, SKOV-3 cells are known to express chemokine receptors for MGSA/GRO$\alpha$. The C-terminal peptide of MGSA/GRO$\alpha$, however, as shown in Roby *et al.* does not bind to this receptor, since the paper states that the conjugate does not bind to SKOV-3 cells. Accordingly, the finding in Roby *et al.* that its conjugate allegedly binds to melanoma cells, but not to SKOV-3 cells, conclusively demonstrates that its conjugates do not bind to chemokine receptors. Roby *et al.* (1995), cited in Roby *et al.*, states (see, *e.g.*, page 797) that the receptor on melanoma cells for the C-terminal peptide of MGSA/GRO$\alpha$ and the chemokine receptor on neutrophils (immune cells) are different.

In addition, as described in the attached DECLARATION and demonstrated in the attached papers (see, *e.g.*, Clark-Lewis *et al.* (1994) *J. Biol. Chem. 269*:16075-16081; Clark-Lewis *et al.* (1991) *J. Biol. Chem. 266*:23128-34; Zhang *et al.* (1991) *J. Biol.Chem. 269*:15918-15924; and Roby *et al.* (1995) *Biochem. Biophys. Res. Commun. 206*:792-798), the C-terminal alpha helix of MGSA/GRO$\alpha$ does NOT bind to chemokine receptors. This further demonstrates that the conjugates of Roby *et al.* do not target cells that express chemokine receptors.

Furthermore, as described in the DECLARATION and supported by the kinetic data in Roby *et al.*, the conjugates of Roby *et al.* are not internalized by virtue of binding to whatever receptors it binds on melanoma cells. Neither Roby *et al.* reference suggest what receptors on melanoma cells are responsible for binding of the C-terminal peptide, except that it is not the chemokine receptor present on neutrophils nor on SKOV-3 cells. As the DECLARATION states, it is likely that the conjugates of Roby *et al.* are sequestered by virtue of low affinity binding to glycosaminoglycans (GAGS) including heparin and heparan sulfate, chondroitin sulfate and dermatan sulfate (see, *e.g.*, Proudfoot *et al.* (2001) *J. Biol. Chem. 276*:10620-26). which expressed to a varying

degree on the surface of cells and are not internalized. By virtue of this low affinity binding, the conjugates of Roby *et al.* are sequestered and enter the daunorubicin enters cells via a diffusion mechanism. As described in the DECLARATION, the high concentrations of drug needed in the short term experiments and the need for long term exposure is far more consistent with cellular uptake of the drug by diffusion rather than by internalization.

It is noted that even without consideration of the DECLARATION, the facts that it is known that the N-terminus of chemokines are required for chemokine receptor binding and that Roby *et al.* shows that its conjugates, which contain the C-terminus of the polhypeptide, do not bind to SK-03 cells, which express chemokine receptors to which MGSA/GRO$\alpha$ should bind, but appears to bind to melanoma cells, indicates that its conjugates do not contain a chemokine receptor targeting agent.

Thus, Roby *et al.* does not provide a conjugate of a chemokine receptor targeting agent and a targeted agent. The targeting agent does not bind to chemokine receptors, as evidenced by the failure to bind to MGSA/GRO$\alpha$ receptors present on SKOV-3 cells. Furthermore, the conjugates of Roby *et al.* are not internalized by virtue of binding to such receptors.

Furthermore, Roby *et al.* provides no disclosure, teaching or suggestion of a method for targeting immune cells or treating inflammatory disorders or secondary tissue damage. Melanoma is a cancer and melanoma cells are tumor cells not immune cells.

**Anticipation analysis**

All claimed methods target conjugates that contain chemokine receptor targeting agents to immune cells that express chemokine receptors. Roby *et al.* discloses conjugates of a peptide that appears to bind to a non-chemokine receptor on melanoma cells, which are not immune cells. Therefore, since Roby *et al.* does not disclose every element as claimed, it does not anticipate any of the pending claims.

**Non-Obviousness analysis**

**Relevant Law**

[I]n order to establish a *prima facie* case of obviousness, there must be evidence, preferably a teaching, suggestion, incentive or inference from the cited art or in the form of generally available knowledge that one of ordinary skill would have been led to modify the relevant teaching to arrive at what is claimed. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. *Stratoflex Inc. v Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 USPQ 1783 (Fed. Cir. 1992).

**Claims**

The rejected claims are summarized above.

**Analysis**

Roby *et al.* does not provide any teaching or suggestion that would have lead one of ordinary skill in the art to do that which applicant has done. There is no suggestion in Roby *et al.* for modification of its methods.

As discussed above, Roby *et al.* purports to teach a method for targeted delivery of a chemotherapeutic agent to melanoma cells presumably for treatment of malignant melanoma. There is no teaching or suggestion in Roby *et al.* for modification of its methods for targeting any agent to immune cells nor for treatment of disorders that share an underlying common pathology associated with inflammatory responses or secondary tissue damage associated with activation, proliferation and migration of immune cells.

As discussed above, not only is the method of Roby *et al.* (treatment of cancer by delivery of chemotherapeutic agents to cancer cells) completely

different from the instant methods (delivery of agents to immune cells), the data in Roby *et al.* belies its own conclusions. Not only do the conjugates of Roby *et al.*, which include a peptide from the C-terminus of MGSA/GRO$\alpha$, which does not bind to chemokine receptors, the data suggests that its conjugates are not internalized but deliver the drug by diffusion.

As discussed above, claim 29 and dependents are directed to a method for treating pathological conditions by **treating the underlying pathology associated with inflammatory responses and secondary tissue damage associated with activation, proliferation and migration of immune effector cells** by inhibiting activation, proliferation or migration of immune effector cells. Claim 35 and dependents are directed to a method of targeting agents to immune effector cells; claim 40 and dependents are directed to a method of treating secondary tissue damage; claim 72 and dependents are directed to methods of inhibiting proliferation, migration or activation of immune cells; and claim 86 and dependents are directed a method of treating a disease or disorder associated with an inflammatory response by identifying immune cells that are activated in the disease or disorder and inhibiting proliferation, migration or activation of the immune cells.

Thus, as noted, all claims are directed to methods that involve inhibiting proliferation, migration or activation of immune cells for treatment of an inflammatory response. Cancer cells are not immune cells. There is no disclosure (or suggestion) in Roby *et al.* for treatment of immune cells nor for substitution of immune cells for cancer cells or modification of its method. Thus, Roby *et al.* does not provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. *Stratoflex Inc. v Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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For: *METHODS AND COMPOSITIONS FOR TREATING SECONDARY TISSUE DAMAGE AND OTHER INFLAMMATORY CONDITIONS AND DISORDERS*

Art Unit: 1647

Examiner: Landsman, R.

I hereby certify that this paper and the attached papers are being deposited with the United States Postal Service as first class mail in an envelope addressed to:

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07/15/2003
Date

Stephanie Seidman

**MARKED-UP CLAIMS (37 C.F.R. § 1.121)**

Please amend claims 29, 35 and 89 as follows:

29. (Thrice Amended) A method for treating pathological conditions by treating the underlying pathology associated with inflammatory responses and secondary tissue damage associated with activation, proliferation and migration of immune effector cells by inhibiting activation, proliferation or migration of immune effector cells, comprising administering a conjugate to an animal whereby activation, proliferation, migration of the immune effector cells is inhibited wherein:

the conjugate comprises a targeted agent or a portion thereof and a chemokine receptor targeting agent or a portion thereof sufficient to bind to [the] a chemokine receptor on immune effector cells and facilitate internalization of the conjugate;

the chemokine receptor targeting agent is a chemokine, an antibody that specifically binds to a chemokine receptor or a fragment of the chemokine or

antibody, wherein the chemokine, antibody or fragment thereof binds to the receptor and internalizes the targeted agent in a cell;

the targeted agent or portion thereof, when internalized in a cell, alters metabolism or gene expression in the cell, regulates or alters protein synthesis in the cell, inhibits proliferation of the cell or kills the cell; and

the conjugate binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor.

35. (Twice Amended) A method of targeted delivery of an agent into cells that express chemokine receptors, comprising associating the agent with a chemokine receptor targeting agent, whereby:

the chemokine receptor targeting agent binds to a chemokine receptor expressed on the cells; and

the agent is internalized by the cells, wherein the cells are immune effector cells.

89. (Amended) The method of claim [38] 57, wherein the chemokine receptor targeting agent is selected from the group consisting of IL-8, GCP-2, GRO-$\alpha$, GRO-$\beta$, GRP-$\gamma$, ENA-78, PBP, CTAP III, NAP-2, LAPF-4, MIG, PF4, IP-10, SDF-1$\alpha$, SDF-1$\beta$, SDF-2, MCP-1, MCP-2, MCP-3, MCP-4, MCP-5, MIP-1$\alpha$, MIP-1$\beta$, MIP-1$\gamma$, MIP-2, MIP-2$\alpha$, MIP-3$\alpha$, MIP-3$\beta$, MIP-4, MIP-5, MDC, HCC-1, LD78$\beta$, eotaxin-1, eotaxin-2, I-309, SCYA17, TARC, RANTES, DC-CK-1, lymphotactin, and fractalkine.